

EXHIBIT D

**UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF WEST VIRGINIA
CHARLESTON DIVISION**

IN RE: ETHICON, INC., PELVIC REPAIR SYSTEM PRODUCTS LIABILITY LITIGATION	Master File No. 2:12-MD-02327 MDL 2327 JOSEPH R. GOODWIN U.S. DISTRICT JUDGE
THIS DOCUMENT RELATES TO WAVE 2 CASES	

GENERAL EXPERT REPORT OF MICHAEL KARRAM MD FACOG FPMRS

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General TVT/TVT-O Report Prepared by Michael Karram MD FACOG FPMRS

Education, Training and Experience:

I am nationally and internationally known in the field of gynecologic surgery and advanced pelvic surgery. As an expert at treating both stress incontinence and pelvic organ prolapse, I have extensive experience using native tissue and augmented repairs. I have been performing TVT since 1998 and have experience with polypropylene retropubic, transobtrurator, and single incision slings. I have also performed a large number of mesh augmented pelvic organ prolapse surgeries.

A chronology of my education, training and experience is outlined below:

1973:	BS	Ohio State University Columbus, Ohio
1978:	MD	Cairo University Faculty of Medicine (Honors) Cairo Egypt
1979-80:	Internship	Case Western Reserve Cleveland Ohio
1980-84:	Residency	Good Samaritan Hospital Cincinnati, Ohio
1983:	Two week clerkship in Urogynecology with Dr. Donald Ostergard	
		Long Beach Memorial Hospital
1984-2001:	Obstetrics and Gynecology Private Practice	Cincinnati, Ohio
2001-Pres:	Gynecology Practice focusing on gynecologic surgery and	

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Urogynecology

1986: Board Certification, American College of Obstetrics and Gynecology

1986: Diplomate, American Board of Obstetrics and Gynecology

2014: Board Certification, Female Pelvic Medicine and Reproductive
Surgery

1998-Pres: Director, Urogynecology Seven Hills Women's Health Centers
Cincinnati, Ohio

2013-Pres: Director, Fellowship Minimally Invasive Gynecologic Surgery,
Christ Hospital Cincinnati, Ohio

2015-Pres: Medical Director Pelvic Floor Center Mercy West Hospital
Cincinnati, Ohio

1998-2013: Consultant, Proctor, Preceptor and Trainer for Ethicon/Gynecare

2000-Pres: Consultant, Proctor, Preceptor and Trainer for American Medical
Systems (Astora)

2013: Presenter at AUGS meeting

2015: Presenter at AUGS meeting

I am a member of the following organizations:

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American Urogynecologic Society (AUGS)

International Urogynecologic Association (IUGA)

American Association of Gynecologic Laparoscopists (AAGL)

As a consultant for the above listed companies I participated as lead faculty at many sling courses and mesh augmented prolapse courses. These courses included a didactic portion, a cadaver training portion, the potential risks and benefits of the devices, the IFU, professional education materials, medical literature, and my own clinical experience involving mid-urethral slings. A lengthy discussion on indications, techniques, complications, management of complications and consenting patients correctly would follow each session. Upon completing these course participants were well versed in:

- Patient selection
- Correct consent process
- Understanding the IFU of the product/products
- Surgical technique
- Implant the procedure completely on the cadaver
- Understand possible complications and how to manage them
- When to refer complicated or difficult patients

I have been performing incontinence surgery my entire career, and have employed all the surgical procedures. I have found TVT and TVT-O to be most beneficial to patients. Both have excellent results, are a minimally invasive procedure, have quick patient recover, are very reproducible, and have excellent outcomes. Additionally, I have extensive experience teaching residents and fellows on the risks and benefits of surgical treatment for stress urinary incontinence and pelvic organ prolapse, including training on the Instructions for Use (IFU). I am the Director of the Minimally Invasive Gynecology Fellowship at The Christ Hospital in Cincinnati, Ohio.

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There is no comparison to the more invasive techniques we have used prior to the TVT. Since it was cleared by the FDA in 1998 it has been my primary surgery unless clinical situations dictate differently. I have taught this procedure to many surgeons both nationally and internationally, and have personally performed over 2000 slings. Because of all the reasons stated, I will continue to use TVT as my preferred method to surgically correct stress urinary incontinence (SUI). In summary, in my opinions discussed below, the TVT and TVT-O's design and material are reasonably safe for their intended use and the Instructions for Use adequately and appropriately warns physicians trained in the surgical treatment of stress urinary incontinence of the potential adverse reactions associated with these devices. A listing of the materials I've reviewed is attached. This list contains the company documents, medical literature, and other materials relating to TVT and TVT-O that I have reviewed and relied on in forming my opinions. All of my opinions are based on my review of the scientific and medical literature, professional society statements, my communications with other pelvic floor surgeons, my involvement in professional education and preceptorships, and my education, training and experience. All of my opinions are held to a reasonable degree of scientific and medical certainty. I have reviewed the reports of the Plaintiffs' experts, and I reserve the right to amend this report and any of my opinions upon receiving additional information or materials.

My hourly rate for review of materials is \$500.00 per hour. In the last four years I've testified in the following cases:

Sharon Boggs et al. v. Ethicon, Inc., et al.; In The United States District Court For The Southern District Of West Virginia Charleston Division; Case No. 2:12-cv-00368

Donna Massey et al. v. Ethicon Inc. et al.; In The United States District Court For The Southern District Of West Virginia Charleston Division; Case No. 2:12-cv-00880

Paula Kriz et al v. Ethicon, Inc. et al.; In The United States District Court For The Southern District Of West Virginia Charleston Division; Case No. 2:12-cv-00938

Margaret Kirkpatrick v. Ethicon, Inc., et al.; In The United States District Court For The Southern District Of West Virginia Charleston Division; Case No. 2:12-cv-00746

Miranda Patterson v. Ethicon, Inc., et al.; In The United States District Court For The Southern District Of West Virginia Charleston Division; Case No. 2:12-0481

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Thelma Wright v. Ethicon, Inc. et al. ; In The United States District Court For The Southern District Of West Virginia Charleston Division; Case No. 2:12-cv-1090

History of Urinary Incontinence:

It is estimated that 25%-75% of women will report some form of urinary incontinence. Minassian et al. (2008) reported that 23%-38% of the female populations in the United States older than age 20 admit to symptoms of stress urinary incontinence. Approximately 16% of patients report their incontinence to be of moderate severity. It is estimated that 7% -10% perceive the SUI as severe. Analysis of Medicare data suggests that only approximately 10% of women diagnosed with SUI undergo surgical correction. Based on population growth charts, it is estimated that the number of women with urinary incontinence will increase from 18 million to 28 million women from 2010-2050.

The pathophysiology of SUI is related to the anatomic position and health of the urethra. Anatomically, the urethra has to be in the right position and well supported during times of stress or strain. If these conditions are not met, then there is excess movement of the urethra and you have a condition of hypermobility. The urethra has a blood and nerve supply that keep its' functional integrity intact. Disruption to the integrity will lead to a urethra that cannot close effectively a condition called lead pipe urethra. This is commonly labeled intrinsic sphincter deficiency (ISD).

Risk Factors for SUI:

Risk factors for SUI can therefore be those that affect one or both of the above described mechanisms. Multiple risk factors have been proposed and studied. These include age, parity, vaginal delivery, hysterectomy, pelvic and vaginal surgery, obesity/BMI, diabetes, hormone replacement therapy, hysterectomy, physical activity, smoking, diet, other medical conditions, and family history (genetic predisposition).

Work-up of the Incontinent Patient:

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The workup for an incontinent patient involves demonstration of incontinence on a cough stress test, normal post void residual, rule out urinary tract infection, a positive Q-tip test and a normal voiding pattern. The Q-tip test is performed by placing a Q-tip in the urethra at the level of the urethra-vesical junction (bladder neck). The angle of the Q-tip to the floor is then measured both at rest and as the patient coughs and strains. If the angle is between 30 and 45 degrees or greater, this indicates a hypermobile urethra. An angle that is less than 30 degrees or non-existent indicates a non-mobile urethra. This information is important when deciding what therapy is used for SUI. In cases that are more complicated, there is a question of overactive bladder associated with the SUI, or to diagnose intrinsic sphincter deficiency, the physician may elect to perform urodynamic testing.

Management of SUI:

The management of SUI has evolved dramatically, both from a patient and surgeons perspective. Historically, patients would not seek treatment because they were told ‘this is a natural part of aging, you just have to live with it’. Or, ‘there is no effective treatment and the treatments that are available are complicated, require long recovery, and always fail’. Many women suffered in silence because of these beliefs.

As women and their healthcare providers became more informed and technology progressed many patients actively pursued management of their condition. The management was either non-surgical or surgical. Women who were not affected by their condition from a quality of life aspect usually did nothing or tried to conservatively manage their issues. This included fluid restriction, frequent bathroom visits, avoiding activities that precipitated incontinence episodes, and wearing absorbent pads. There were also incontinence pessaries and other mechanic devices that could be used as an obstructive management of incontinence.

Surgery remained the mainstay for the treatment of SUI; however it has significantly evolved over the years due to innovation and better understanding of the disorder. It is well known by all pelvic floor surgeons that any surgery for stress urinary incontinence or pelvic

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organ prolapse, with or without the use of mesh, can potentially cause complications that can be temporary or permanent, including but not limited to: pelvic pain, dyspareunia (pain with sexual intercourse), scarring, vaginal narrowing, leg/groin pain, urinary retention and other voiding problems. Historically, there have been many surgeries that have been used to treat SUI, culminating in the mid-urethral sling used today. Most experts in the field of female pelvic medicine and reconstructive surgery agree that the mid-urethral sling is the standard of care for the treatment of SUI. Support is based on an abundance of scientific data. The American Urogynecologic Society (AUGS) performed a worldwide survey of its members asking ‘what is your procedure of choice for surgical management of SUI.’ The overwhelming majority answered a mid-urethral synthetic sling.

Surgical procedures for SUI:

Anterior repair/cystocele repair: For many years this was the procedure used to treat SUI. It was designed to repair an anterior vaginal wall defect that allowed the bladder to prolapse through the weakened support. Kelly plication sutures were used to repair the pubo-cervical septal defect and support the proximal urethra and bladder neck. Results were poor due to many factors: poor diagnostic techniques, inadequate understanding of the anatomic problem, patient selection, and surgical technique.

Needle suspension procedures (Stamey, Gittes, and Peyrera)

These procedures attempted to suspend the bladder neck via a vaginal approach. This was achieved by either using sutures or a graft to suspend the bladder neck. These procedures were more popular in the urology community. Results were very difficult to interpret due to the different surgical techniques, patient selection, and pre-operative evaluation. These techniques never gained popularity due to the inconsistent results.

Retropubic operations for SUI (Marshall Marchetti Krantz (MMK), Burch Colposuspension and Paravaginal defect repair).

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These procedures initially were performed through an abdominal incision and then they were later modified and performed laparoscopically. Both the Burch and MMK procedures require “direct access” to the tissues surrounding the bladder and urethra and are deemed “major” surgical cases that involve an abdominal incision and wide vaginal dissection. This extensive surgery is associated with a significant risk of wound complications, bleeding, and genitourinary tract injury including damage to the ureter, bladder, and urethra (Stanton 1985). Median surgical times are typically in excess of 2 hours, hospital stay averages 2-3 days, and prolonged catheter drainage is usually required. Most of my young, ambulatory women with primary stress incontinence are unwilling to take 6 weeks off from work and their family obligations to recover from these surgical interventions.

In 2002 the noninferiority of TVT compared to the Burch colposuspension was demonstrated in a randomized controlled trial. Ward et al. (2002). The follow-up on this study lasted five years. Ward et al. (2008). The laparoscopic Burch procedure was compared to TVT with a 20 month mean follow-up time in Paraiso’s (2004) randomized controlled trial. This trial demonstrated that TVT had shorter operating times and great objective and subjective cure rates for urodynamic stress incontinence that was found with the laparoscopic Burch procedure.

Additional studies have shown that the Burch colposuspension’s efficacy declines in the long-run with significant complications (both intra and post-operatively). These complications include prolapse development, suprapubic pain, groin pain, dyspareunia, voiding dysfunction and wound complications. (See Richter HE, et al. *Urinary Incontinence Treatment Network. Patient related factors associated with long-term urinary continence after Burch colposuspension and pubovaginal fascial sling surgeries*. J Urol. 2012 Aug; 188(2):485-9; Demirci F. et al. Long-term results of Burch colposuspension. Gynecol Obstet Invest. 2001; 51(4):243-7; Chaliha C, et al. *Complications of surgery for genuine stress incontinence*. Br J Obstet Gynaecol. 1999 Dec; 106(12):1238-45; Alcalay M, et al. *Burch colposuspension: a 10-20 year follow up*. Br J Obstet Gynaecol. 1995 Sep;102(9):740-5. Erratum in: Br J Obstet Gynaecol 1996 Mar; 103(3):290; Kjølhede P. *Long-term efficacy of Burch colposuspension: a 14-year follow-up study*. Acta Obstet Gynecol Scand. 2005 Aug; 84(8):767-72).

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The MMK was an abdominal retropubic procedure that suspended the peri-urethral tissue to the back of the symphysis pubis. The sutures were anchored into the periosteum of the bone. Problems were osteitis pubis, damage to the blood and nerve supply of the urethra, and a non-mobile urethra.

The paravaginal repair was a procedure to repair the lateral tear between the vagina and lateral pelvic sidewall in an attempt to recreate the vaginal hammock that supported the urethra. Results varied and this procedure never gained universal adoption in the surgical management of SUI.

The Burch was a procedure which supported the urethra by elevating the paravaginal fascia at the mid urethra and bladder neck to coppers ligament. Prior to TVT, this procedure became the gold standard to which all incontinence procedures are compared. However, this was an abdominal procedure that required hospitalization and long recovery. It is considered major surgery. The results were very good but it failed in the low pressure urethra or the severe intrinsic sphincter deficiency patient. Patients also required a suprapubic catheter to manage post-operative voiding.

Slings are a vaginal procedure designed to re-support the mid-urethra to correct SUI. They can be cadaveric fascia, rectus fascia, biologic material, or synthetic polypropylene mesh. Cadaveric fascia was used for a short time but results were very inconsistent and it lost its popularity to the rectus fascia sling which is still used under certain conditions.

Rectus fascia slings are used under certain conditions when a patient cannot tolerate mesh or does not want a mesh sling. It is a more difficult operation, requires a more extensive dissection, and result vary based on technique and tensioning. Also, the fascial slings are more bladder neck then mid-urethral. Since fascial slings are placed at the bladder neck and not the mid-urethra, they are more obstructive in nature and therefore susceptible to a higher risk of post-operative complications. These are urinary retention, voiding dysfunction, overactive

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bladder symptoms and irritative bladder problems. These procedures are more invasive because they also require an abdominal incision to harvest the patient's fascia.

TVT (Tension free vaginal tape): Mid-urethral slings like TVT and TVT-O have revolutionized the surgical approach to SUI management and have become the gold standard for treating SUI (See Serati M, et al. Surgical treatment for femal stress urinary incontinence: what is the gold-standard procedure? Int Urogynecol J Pelvic Dysfunct. 2009 Jun; 20(6);619-21). TVT and TVT-O have the advantages of: a minimally invasive outpatient procedure, results comparable to the Burch procedure, 30 min or less operating time, and very rapid patient recovery. The results are reproducible, and it works well in both the hypermobile and intrinsic sphincter deficiency urethra. The procedure is based on the "integral theory" proposed by Ulmsten and Petros in 1995. The theory is based on the presumption that the pubo-urethral ligaments support the mid-urethra and attach to the pubic bones, acting as a backboard. The backboard allows compression of the mid-urethra during increased intraabdominal pressure thus maintaining continence. The concept states that absence of the backboard support causes loss of the watertight seal and SUI develops. By placing a supportive material under the mid-urethra the backboard action can theoretically be replicated. In designing the tension free vaginal tapes, certain goals were set:

1. To avoid the need for a major abdominal incision and use the vagina as the primary route of surgical access
2. Introduce a stable hammock of support at the level of the mid-urethra and not the bladder neck
3. Provide urethral closure only during episodes of increased intra-abdominal stress and not at rest, thereby reducing the risks of voiding dysfunction
4. Use a sling material that was safe, durable, and did not require harvesting of native tissue

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5. Design a system that required minimal tissue dissection, thereby maximally preserving the nerves and surrounding supportive tissue.

6. Design a procedure and technique that is highly reliable and reproducible

TOT (Transobturator sling): Because retropubic TVT required a blind passage through the retropubic space, inadvertent bladder perforation occurs in 3%-5% of cases. If there is inadvertent bladder perforation, it does not cause any permanent damage. Routine cystoscopy is performed on all sling procedures and a perforation would be picked up immediately. The TVT introducer would be removed, the urethral catheter guide would displace the bladder and urethra away from the area, and the introducer would be placed more lateral to the first pass. Again, cystoscopy is performed and if correct placement is assured then the sling is placed. Post-operative management is exactly the same and we do not require prolonged catheterization in these situations. Also, vascular and bowel injuries, albeit rare, were reported that resulted in significant morbidity and mortality. In hope of avoiding these complications, Delorme described the trans-obturator technique in 2001. There is an abundance of peer review data that substantiates the effectiveness of the TVT-O in the treatment of SUI. With the inside out TVT-O the chance of experiencing groin, inner thigh or leg pain is much less than the outside in approach. The reason being less peri-urethral dissection is needed to pass the helical introducer. The muscles that are penetrated with the outside in TOT are gracilis, adductor brevis, obturator externus, obturator membrane and obturator internus. Sometime the adductor magnus is penetrated as well. With the TVT-O it is easier to avoid large muscle penetration due to the design of the product. The less muscle penetration the fewer groin and thigh pain. The drawback to the TOT is the fact that the results with ISD patient are better with retropubic slings than TOT. Most skilled surgeons will choose a retropubic approach for ISD and a TOT approach for mixed incontinence unless there is mixed with severe ISD.

Both the TVT and TVT-O include a protective sheath around the mesh. This sheath not only protects the mesh during the implant procedure (and thus minimizes the risk of infections

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developing post-operatively) but it also helps ensure a smooth and properly tensioned placement of the mesh under the mid-urethra.

Photo of Groin Muscles

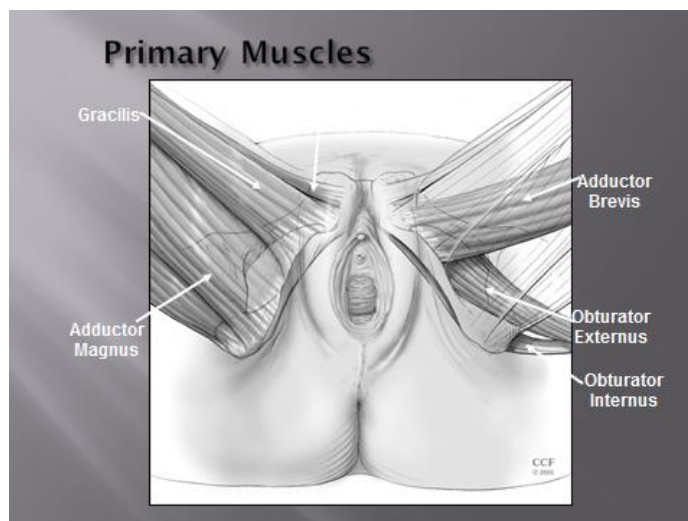
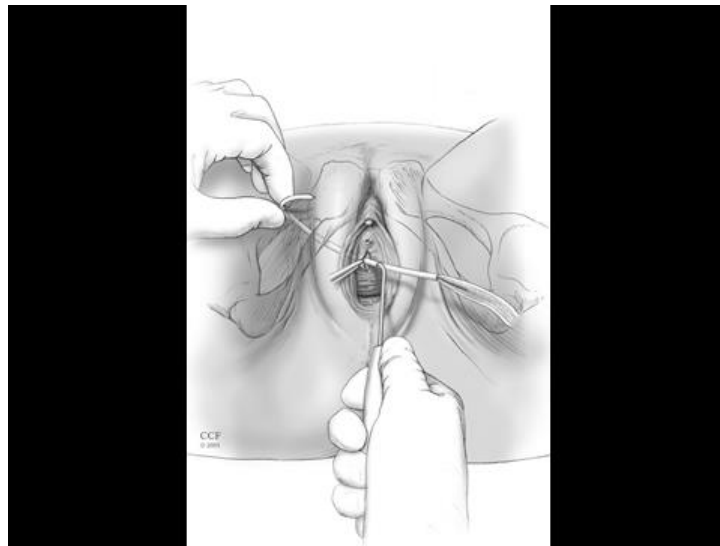
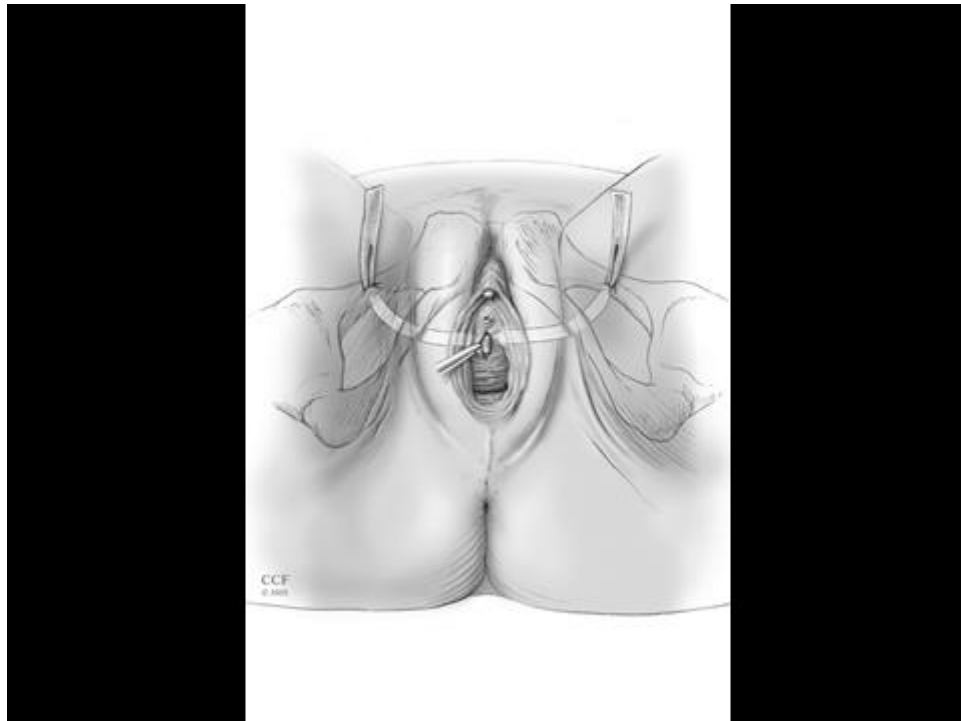


Photo of TVT-O Trajectory

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TVT-O Final Placement



Tommaselli's recent meta-analysis verifies that retropubic slings are not superior to

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transobturator slings. This meta-analysis surveyed the long-term outcomes of retropubic slings and mid-term outcomes of obturator slings and included 39 studies (11 RCT's and 28 non-randomized studies) covering 6406 women. This analysis found that both retropubic and obturator slings have high objective and subjective cure rates in the long and medium term. It also found that vaginal extrusions (which can often be treated conservatively) were reported at 2.1% and 2.7% for retropubic and obturator slings, respectively. Pain lasting longer than the immediate post-operative period was reported at a rate of 0.3% for retropubic slings and 1.2% for obturator slings. The authors concluded that these slings have high efficacy, a high safety profile and a low risk of complications, which are "seldom severe". Significantly, this analysis found that there was not a significant difference between retropubic and obturator slings in patient's post-operative pain. Tommaselli GA, et al. *Medium-term and long-term outcomes following placement of midurethral slings for stress urinary incontinence: a systematic review and metaanalysis*. Int Urogynecol J. 2015 May 20.

The Society of Gynecologic Surgeons (Schimpf, 2014) recently surveyed the medical literature and conducted a meta-analysis that analyzed the surgical treatment of SUI. This meta-analysis found no significant difference in efficacy between obturator and retropubic slings. It also concluded that slings like TVT and TVT-O are first line treatment options compared to a Burch or pubovaginal slings. Also of significance, this analysis found a 1.9% rate of return to the operating room for erosion and 1.2% return to operating room for urinary retention. In 2015 Unger found a 2.7% rate of overall reoperation, with pain and dyspareunia being a reason for mesh removal in only 0.2% of patients. Welk also found in 2015 a 2.2% surgical intervention rate for mesh complications and a 3.3% 10 year overall rate of complications. These low rates of complication requiring follow-up surgery are also consistent with my own surgical experience.

Data Comparing TVT and TVT-O (TOMUS Trial)

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	TOT	TVT	p
Major Bleeding	4%	2%	.16
Retropubic hematoma	2%	1%	.44
Bladder Injury	0%	5.1%	.004
Bowel Injury	0%	0%	1.00
Nerve Injury	2%	1%	.44

From Barber 2006

	TOT	TVT	p
Leg Comp.	0.5%	0.5%	.89
Voiding Dys.	2.9%	8.9%	.01
Postop Anti-Cholinergics	6.3%	14%	.05
UTI	7.4%	12.7%	.08
Mesh erosion	0.5%	1%	.99
Reop. for SUI	1.5%	2.4%	.51

Photo of transobturator sling:

Alternative procedures:

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There have been attempts to modify the procedure by using freezing or radiofrequency to treat the periurethral tissue and recreate the support. None of these procedures have gained support. The results are poor and they have a higher complication/failure rate.

Periurethral bulking agents: This is a cystoscopic directed procedure where certain materials are injected into the mucosa of the urethra at the level of the urethra-vesical junction. It attempts to increase urethra resistance by coapting the urethral mucosa. It is not typically used as a primary procedure but more as an adjunct. It does not work well in the hypermobile urethra and may help in the patient with ISD. There is debate over the type of material to be used hence the inaccuracy in the results.

Results and References:

The TVT and TVT-O procedures are among the most studied procedures in gynecology. The literature supports its use overwhelmingly as safe, minimally invasive, with excellent results comparable to any other procedure, has high patient satisfaction, and strong clinical outcomes. Complication rates are low compared to the more invasive procedures. The results are very reproducible regardless of the surgeon performing the procedure. Plaintiffs' contention that TVT and TVT-O are not safe fail to account for the fact that the highest form of evidence—systematic reviews and meta-analysis have consistently found TVT and TVT-O to be safe with low rates of complications.

The Cochrane Library published a meta-analysis (based on 62 studies) showing short-term cure rates between 73% and 82%. The largest randomized controlled study comparing retropubic and transobtrurator slings (Trial of Mid-Urethral Slings [TOMUS]) showed subjective and objective cure rates of 62% and 78% respectively. Two prospective cohort studies reporting 7-year and 11-year follow-up reported subjective cure rates of 85% and 77% respectively. The 2009 Cochrane review summarized its findings in this abstract:

“Sixty-two trials involving 7,101 women were included. The quality of evidence was moderate for most trials. Minimally invasive synthetic suburethral sling operations

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appeared to be as effective as traditional suburethral slings [8 trials, n=599, risk ratio (RR) 1.03, 95% confidence interval (CI) 0.94--1.13] but with shorter operating time and less postoperative voiding dysfunction and de novo urgency symptoms. Minimally invasive synthetic suburethral sling operations appeared to be as effective as open retropubic colposuspension (subjective cure rate at 12 months RR 0.96, 95% CI: 0.90--1.03; at 5 years RR 0.91, 95% CI: 0.74--1.12) with fewer perioperative complications, less postoperative voiding dysfunction, shorter operative time, and hospital stay but significantly more bladder perforations (6% vs. 1%, RR 4.24, 95% CI: 1.71--10.52). There was conflicting evidence about the effectiveness of minimally invasive synthetic suburethral sling operations compared to laparoscopic colposuspension in the short term (objective cure, RR 1.15, 95% CI: 1.06--1.24; subjective cure RR 1.11, 95% CI: 0.99--1.24). Minimally invasive synthetic suburethral sling operations had significantly less de novo urgency and urgency incontinence, shorter operating time, hospital stay, and time to return to daily activities. A retropubic bottom-to-top route was more effective than top-to-bottom route (RR 1.10, 95% CI: 1.01--1.20; RR 1.06, 95% CI: 1.01--1.11) and incurred significantly less voiding dysfunction, bladder perforations, and tape erosions. Monofilament tapes had significantly higher objective cure rates (RR 1.15, 95% CI: 1.02--1.30) compared to multifilament tapes and fewer tape erosions (1.3% vs. 6% RR 0.25, 95% CI: 0.06--1.00). The obturator route was less favorable than the retropubic route in objective cure (84% vs. 88%; RR 0.96, 95% CI: 0.93--0.99; 17 trials, n=2,434), although there was no difference in subjective cure rates. However, there was less voiding dysfunction, blood loss, bladder perforation (0.3% vs. 5.5%, RR 0.14, 95% CI: 0.07--0.26), and shorter operating time with the obturator route.”

I agree with these findings and they are consistent not just with my surgical experience with thousands of patients, but also with my review of medical literature and other systematic analyses. More recently, the 2015 Cochrane review concluded that mid-urethral sling procedures like TVT and TVT-O, “have been the most extensively researched surgical treatment for stress urinary incontinence (SUI) in women and have a good safety profile. Irrespective of the

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routes traversed, they are highly effective in the short and medium term, and accruing evidence demonstrates their effectiveness in the long term. This review illustrates their positive impact on improving the quality of life of women with SUI.” The authors also found that the “reported occurrence of problems with sexual intercourse including pain was low, and leakage of urine during intercourse are improved following insertion of these tapes.” This most recent Cochran meta-analysis found the following low rates of complications:

- Bladder perforation: 2.7% to 3.9% of cases.
- Reoperation rates relating to tape insertion or postoperative voiding dysfunction: 1.6% to 2.4%.
- Urinary retention: 1.6%.
- Pelvic hematoma: 0.7% to 1.9%
- Infection rate: 0.7%.
- Vaginal tape erosion/extrusion: 1.5%.
- Groin pain: 0.4%

These low rates of complications demonstrate that TVT and TVT-O are both safe and effective treatment options. These rates are also consistent with my own clinical experience and my review of the medical literature. Furthermore, published meta-analysis like the Cochrane review, Shimpf 2014 and Tommasselli 2015 demonstrate that the complications associated with TVT and TVT-O are widely published and widely known outside of any materials disseminated by Ethicon.

TVT and TVT-O are the most studied incontinence procedures, with over 150 randomized controlled trials and multiple long-term studies supporting their safety, efficacy, and reproducibility. Long-term TVT studies include the following: Nilsson CG, et al. *Eleven years*

**MICHAEL KARRAM MD FACOG FPMRS
UROGYNECOLOGY AND GYNECOLOGIC SURGEON
SEVEN HILLS WOMENS HEALTH CENTERS
CINCINNATI, OHIO**

prospective follow-up of the tension-free vaginal tape procedure for treatment of stress urinary incontinence. Int Urogynecol J Pelvic Floor Dysfunct. 2008 Aug;19(8):1043-7; Liapis A, et al. *Long-term efficacy of tension-free vaginal tape in the management of stress urinary incontinence in women: efficacy at 5- and 7-year follow-up.* Int Urogynecol J Pelvic Floor Dysfunct. 2008 Nov; 19(11):1509-12; Olsson I, et al. *Long term efficacy of the tension-free vaginal tape procedure or the treatment of urinary incontinence. A retrospective follow-up 11.5 years post-operatively.* Int Urogynecol J (2010) 21:679-683; Aigmueller T, et al. *Ten-year follow-up after the tension-free vaginal tape procedure.* Am J Obstet Gynecol. 2011 Nov;205(5):496.e1-5; Groutz A, et al. *Ten-year subjective outcome results of the retropubic tension-free vaginal tape for treatment of stress urinary incontinence.* J Minim Invasive Gynecol. 2011 Nov-Dec;18(6):726-9; Serati M, et al. *Tension-free vaginal tape for the treatment of urodynamic stress incontinence: efficacy and adverse effects at 10-year follow-up.* Eur Urol. 2012 May;61(5):939-46; Heinonen P, et al. *Tension-free vaginal tape procedure without preoperative urodynamic examination: long-term outcome.* Int J Urol. 2012 Nov;19(11):1003-9; Svenningsen R, et al. *Long-term follow-up of the retropubic tension-free vaginal tape procedure.* Int Urogynecol J. 2013 Aug; 24(8):1271-8; Nilsson CG, et al. *Seventeen years' follow-up of the tension-free vaginal tape procedure for female stress urinary incontinence* Int Urogynecol J. 2013 Aug; 24(8):1265-9.

Additionally, the safety and efficacy of TVT-O, to include low complication rates, is well supported by multiple long-term studies. These studies include: Tommaselli GA, et al. *Tension-free vaginal tape-obturator and tension-free vaginal tape-Secur for the treatment of stress urinary incontinence: a 5-year follow-up randomized study.* Eur J Obstet Gynecol Reprod Biol. 2015 Feb; 185:151-5; Tommaselli GA, et al. *Medium-term and long-term outcomes following placement of midurethral slings for stress urinary incontinence: a systematic review and metaanalysis.* Int Urogynecol J. 2015 May 20; Athanasiou S, et al. *Seven years of objective and subjective outcomes of transobturator (TVT-O) vaginal tape: why do tapes fail?* Int Urogynecol J. 2014 Feb; 25(2):219-25. Laurikainen E, et al. *Five-year results of a randomized trial comparing retropubic and transobturator midurethral slings for stress incontinence.* Eur Urol.

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2014 Jun;65(6):1109-14; Serati M, et al. *TVT-O for the treatment of pure urodynamic stress incontinence: efficacy, adverse effects, and prognostic factors at 5-year follow-up.* Eur Urol. 2013 May; 63(5):872-8; Cheng D, et al. *Tension-free vaginal tape-obturator in the treatment of stress urinary incontinence: a prospective study with five-year follow-up.* Eur J Obstet Gynecol Reprod Biol. 2012 Apr; 161(2):228-31; Liapis A, et al. *Efficacy of inside-out transobturator vaginal tape (TVTO) at 4 years follow up.* Eur J Obstet Gynecol Reprod Biol. 2010 Feb; 148(2):199-201.

Company Training:

Ethicon/Gynecare did an excellent job of educating surgeons on the use of their products. As mentioned above in this document, I served as lead faculty on many training sessions. Thus, I have an intimate understanding of what the reasonably prudent pelvic floor surgeon should know about the risks and benefits of pelvic floor procedures, the adequacy of the warnings in IFUs, the management of mesh complications, and the well-known risks that are associated with any pelvic floor surgery. It is common knowledge to pelvic floor surgeons that any surgery for stress urinary incontinence or pelvic organ prolapse, with or without the use of mesh, can potentially cause complications that can be temporary or permanent, including but not limited to: pelvic pain, dyspareunia (pain with sexual intercourse), scarring, vaginal narrowing, leg/groin pain, urinary retention and other voiding problems. Ethicon's professional education process would begin with the representatives in the field surveying qualified surgeons that might be interested in the use of these devices. A qualified surgeon would be a urogynecologist or gynecologist who is experienced and knowledgeable in the surgical management of SUI. Hence, that is a major portion of their practice. They would be given information on the products, the IFUs, and clinical data to review before their training session. The training session would be two days and there would be on Friday night an in depth discussion between faculty and participants' about indications, contraindications, technique, complications and management of the complications. Saturday would be a full day in the cadaver lab 7am-5pm. A didactic presentation followed by a cadaver lab where every participant, under the supervision of the faculty member, would implant the device over and over again until the faculty member and participant were satisfied with the

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objectives. The participants would receive a certificate verifying their attendance at the course. Faculty members would then meet with the Ethicon/Gynecare representatives and give them an evaluation of all the participants, specifically those that were felt to be deficient or weak in their technique or knowledge. Upon departure all participants were given our contact info to call if they had any questions or problems. They were also offered a preceptor to come to their institution and observe with their first few cases if they desired.

To facilitate these training sessions, Ethicon incorporated professional education slide decks into their TVT and TVT-O presentations to doctors (see, for example ETH.MESH.00373310 and ETH.MESH. 00993273). These slide decks not only provided technical guidance on how to perform a TVT or TVT-O procedure, but they also provided pelvic floor surgeons with an overview of success and complication rates of these devices as reported by the medical literature at the time. I have not only reviewed these slide decks, but I have taught other doctors from these decks at past professional education events sponsored by Ethicon.

Surgeon Credentialing:

Credentialing is done by the hospital credentialing committee, not by Ethicon/Gynecare. Every hospital has its own method for credentialing. At our institution, surgeons were credentialed based on their surgical practice, volume and past surgical history. Once they were credentialed they must be observed by an experienced TVT surgeon for their first 5 cases.

Adequacy of Company IFU and Patient Brochures:

Ethicon/Gynecare had very detailed Instruction for Use (IFU) with all their sling products. They are very detailed and self-explanatory on all aspects of the procedures. We also made it a point to go over the IFU in detail during training sessions. They detailed the issues related to warnings and precautions associated with the procedures. All participants were given the IFU as well. The company also offered detailed brochures with resources available to the

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UROGYNECOLGY AND GYNECOLOGIC SURGEON
SEVEN HILLS WOMENS HEALTH CENTERS
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patients. These patient brochures were designed to provide information to a patient—not to take the place of the informed consent between that patient and her doctor.

The IFUs for TVT and TVT-O are designed for pelvic floor surgeons—not patients. For example, TVT’s first IFU states that “This device should be used only by physicians trained in the surgical treatment of Stress Urinary Incontinence.” Based on my review of medical literature, my role as a professional education instructor, my interaction with hundreds of pelvic floor surgeons, my education and training, and my over thirty years of surgical practice, it is my opinion that the TVT and TVT-O IFU and Ethicon’s professional education materials such as the TVT Surgeon’s Resource Monograph adequately describe the risks that are specific or unique to TVT and TVT-O. Moreover, the actual surgical risks and complications (as opposed to warnings about alleged design deficiencies) that plaintiffs’ experts opine should be included in the TVT and TVT-O IFUs are risks that are commonly known to pelvic floor surgeons. I base these opinions on the following:

- The vast body of TVT and TVT-O medical literature that extensively records success and complication rates associated with these devices. With over 1,000 TVT studies, over 150 randomized controlled trials on TVT and TVT-O, and multiple meta-analysis as documented above, no other incontinence product has had its safety profile so well documented as does these two products, which are made of the exact same Prolene mesh material.
- Although I am not a regulatory expert, I have reviewed 21 C.F.R. 801.109(c), which provides for the omission of risk information if “the article is a device for which directions, hazards, warnings, and other information are commonly known to practitioners licensed by law to use the device.” Additionally, the FDA’s “Blue Book Memo” echoes this language, stating that information may not be included in a warning label if “the directions, hazards, warnings, and other information are commonly known to practitioners licensed by law to use the device...”

**MICHAEL KARRAM MD FACOG FPMRS
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- The FDA’s 2013 statement “Considerations about Surgical Mesh for SUI.” This statement, which noted that the “safety and effectiveness of multi-incision slings is well-established in clinical trials that followed patients for up to one year,” also concluded that out of the spectrum of potential complications that a patient can experience following pelvic floor surgery, only mesh erosion/extrusion was unique to a synthetic mesh procedure.¹
- My education, training, and surgical experience, which includes the implantation of over 2,000 slings in addition to the patients I’ve treated who have had slings implanted by other doctors.
- My years of experience training other pelvic floor surgeons in treating SUI and, in particular, in treating SUI with TVT and TVT-O. These training sessions not only allow me to instruct others, but provides me with a forum in which I have received a tremendous amount of feedback about the risks and complications associated with TVT and TVT-O from other pelvic floor surgeons across the country.
- My attendance at various medical conferences and professional society meetings, which include data about the performance of TVT and TVT-O in the hands of a wide variety of pelvic floor surgeons. This data is often presented in the form of oral presentations, abstracts, and posters.

Biocompatibility of mesh:

¹ The FDA concluded in this 2013 statement: “The most common complications reported through MDRs for surgical mesh slings for SUI repair, in descending order of frequency, include: pain, mesh erosion through the vagina (also called exposure, extrusion or protrusion), infection, urinary problems, recurrent incontinence, pain during sexual intercourse (dyspareunia), bleeding, organ perforation, neuro-muscular problems and vaginal scarring. Many of these complications require additional medical intervention, and sometimes require surgical treatment and/or hospitalization. With the exception of mesh erosion, the above complications can occur following a non-mesh surgical repair for SUI.”

**MICHAEL KARRAM MD FACOG FPMRS
UROGYNECOLOGY AND GYNECOLOGIC SURGEON
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The Prolene mesh that comprises TVT is biocompatible with a well-documented history of safe and effective implantation in the pelvic floor. The allegation by many plaintiffs' experts that Prolene mesh is cytotoxic and harmful to pelvic floor tissue is without merit. Polypropylene mesh has been proven to produce a minimal inflammatory reaction in the body, especially when compared to other synthetic materials (Falconer, 2001). The 2015 Cochrane review notes that meshes like Ethicon's Prolene mesh have the "highest biocompatibility:"

Type I mesh has the highest biocompatibility with the least propensity for infection. Differences in their efficacy and complications are likely to be due to several factors including the different knits and weaves of the various tape materials, their biomechanical properties and histological biocompatibility. Pore size affects the inflammatory response and resultant connective tissue formation within and into the mesh, and the rearrangement of materials such as collagen within the mesh structure. Macroporous meshes (pore size in excess of $75 \mu\text{m}$) easily allow macrophages, leukocytes, fibroblasts, blood vessels and collagen to transverse the pores: thus macroporous meshes promote tissue host ingrowth with resultant biocompatibility and low risk of infection (Amid 1997). Monofilament tapes are widely available and now predominate in current clinical practice.

Additionally, the 2014 AUGS/SUFU joint position statement notes the following:

- Polypropylene material has been used in most surgical specialties (including general surgery, cardiovascular surgery, transplant surgery, ophthalmology, otolaryngology, gynecology, and urology) for over five decades, in millions of patients in the US and the world (personal communication with manufacturers of polypropylene suture and mesh). As an isolated thread, polypropylene is a widely used and durable suture material employed in a broad range of sizes and applications. As a knitted material, polypropylene mesh is the consensus graft material for augmenting hernia repairs in a number of areas in the human body and has significantly and favorably impacted the field of hernia surgery. As a

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UROGYNECOLOGY AND GYNECOLOGIC SURGEON
SEVEN HILLS WOMENS HEALTH CENTERS
CINCINNATI, OHIO**

knitted implant for the surgical treatment of SUI, macroporous, monofilament, light weight polypropylene has demonstrated long term durability, safety, and efficacy up to 17 years.

- The monofilament polypropylene mesh MUS is the most extensively studied antiincontinence procedure in history.
- Polypropylene mesh midurethral slings are the standard of care for the surgical treatment of SUI and represent a great advance in the treatment of this condition for our patients.
- This procedure is probably the most important advancement in the treatment of stress urinary incontinence in the last 50 years and has the full support of our organizations which are dedicated to improving the lives of women with urinary incontinence.
- Over 3 million MUS have been placed worldwide and a recent survey indicates that these procedures are used by > 99% of AUGS members.

I agree with the all these statements and other similar conclusions found in other professional society guidelines/statements. They are not only consistent with my own clinical experience treating thousands of women with polypropylene products, but these statements reflect the overwhelming consensus of the medical literature that I have read and reviewed during my career practicing medicine. This past year, Peter Petros published “Creating a gold standard surgical device: scientific discoveries leading to TVT and beyond.” In this piece, he chronicles the development of TVT and why the polypropylene sling was selected as the best option: “By 1996 polypropylene mesh tape had solved the problem of erosions and become universally accepted.” Almost twenty years later, it remains the universally accepted gold standard. As Petros observed regarding the status of polypropylene slings in 2015, “The midurethral sling based on reinforcing the PUL has become the gold standard and is already in the category of Kuhn’s “Normal science”, with hundreds of papers investigating various aspects of the surgery and anatomy.” With this level of consensus in the medical community and medical literature, the allegations that plaintiffs’ experts make about characteristics of Prolene mesh used in TVT

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SEVEN HILLS WOMENS HEALTH CENTERS
CINCINNATI, OHIO**

and TVT-O, which I address below, are without merit and unsupported by the weight of medical science.

Malignant potential of mesh:

The malignant potential of implanted mesh in humans has been raised by plaintiffs. This can be attributed to animal studies done in 1958 by Dr. Oppenheimer. He demonstrated the development of sarcomas in rats implanted with sheets of plastic. However, more recent animal studies implanting monofilament and multifilament polypropylene mesh in mice, did not corroborate these findings. This phenomenon was related to the implanted materials physical traits with discs and sheets including pure metal, polymers, and glass being the most carcinogenic. These solid materials lose their carcinogenicity when they are implanted in porous or woven forms. An epidemiologic study by the International Agency for Cancer Research (IARC) in 2000 concluded that there is no evidence of tumorigenicity of metallic or synthetic implants in humans.

Surgeons at the Cleveland Clinic reviewed their mid-urethral synthetic slings performed between 2004 and 2013. During this period, 2,361 synthetic slings were performed and followed for 5-6 years. No sarcomas were found and their incidence of malignancy after mid-urethral sling was 0%. Their conclusion was there is no support for any association between polypropylene mesh used in mid-urethral slings and the development of malignancy in humans.

Surgeons at the Mayo Clinic reviewed their data from 2002-2012. During this period, 2,474 synthetic slings were placed. Median follow-up was 5 years. Their conclusion was that the development of pelvic malignancy after a mid-urethral synthetic sling is rare and unlikely to be secondary to foreign body reaction from implanted material.

The American Urogynecologic Society (AUGS) and the Society of Urodynamics, Female Pelvic Medicine and Urogenital Reconstruction (SUFU), answered this question by stating ‘Tumors related to the implantation of surgical grade polypropylene for mid-urethral slings in humans have never been reported. There is no compelling evidence supporting human malignant

**MICHAEL KARRAM MD FACOG FPMRS
UROGYNECOLOGY AND GYNECOLOGIC SURGEON
SEVEN HILLS WOMENS HEALTH CENTERS
CINCINNATI, OHIO**

transformation related to polypropylene despite millions of individuals implanted with various forms of this material spanning well over a half century world-wide.’

To date, there is no level I scientific data to conclude there is a correlation between the development of malignancy in humans with the implantation of polypropylene mesh products. They should be considered safe until scientific data proves otherwise.

Pore Size and Weight

Prolene Type I mesh is monofilament and manufactured with a pore size greater than 75 microns. Amid established that a macroporous mesh will have pores that are greater than 75 microns, and this is important for many reasons. Such construction promotes resistance to infection by allowing macrophages to enter the pores. Macrophages cannot enter pores that are less than 10 microns. Such design also allows greater type III collagen deposition, greater capillary penetration, and greater attachment strength. The mesh in TVT and TVT-O has a pore size greater than 1.3mm (Moalli 2008).

Knitted mesh has the highest porosity, lowest volume and largest interstices. Porosity allows the growth of fibroblasts around monofilaments without contraction bridges. This minimizes the foreign body reaction. The flexibility of the fiber in the lightweight macroporous graft facilitates a tension free repair and helps prevent stiffness in the vagina after augmentation.

The biology of prosthetic implant incorporation is accomplished in stages. By day 3 there is inflammation first exudative and then cellular. Polypropylene is the least inflammatory. By day 10 there is fibroblast ingrowth and by week 6 complete ingrowth. The prosthetic strength doubles from week 3 to week 12.

The Prolene TVT mesh is considered to be an Amid Type 1 mesh, and is commonly referred to as large-pore and lightweight mesh. The initial TVT trials with Prolene mesh by Ulmsten, showed no adverse reaction. Specifically, there was no indication of unacceptable rates of mesh infection, rejection, host tissue reaction, or impaired healing. Heavier meshes have

**MICHAEL KARRAM MD FACOG FPMRS
UROGYNECOLOGY AND GYNECOLOGIC SURGEON
SEVEN HILLS WOMENS HEALTH CENTERS
CINCINNATI, OHIO**

greater and more prolonged inflammation. The hundreds of TVT and TVT-O studies since ratify the fact that Prolene mesh used to treat SUI is highly biocompatible and yields low rates of complications and high rates of objective and subjective success. Also, there is evidence of increased cell turnover ongoing inflammation and remodeling at one year. Furthermore, because tissues acting on the mesh can cause the mesh to shrink or contract, the fact that polypropylene meshes elicit a minimal foreign body reaction support my opinion that the mesh in TVT and TVT-O does not contract or shrink in vivo in any clinically significant way. In fact, Nilson 2013 noted that even after 17 years following implant, “there seems to be no shrinkage of the TVT mesh over time...” Lo 2004 also concluded that “The observation of the tape position and characteristics suggests that shrinkage and compromise of the sling does not occur.”

Plaintiffs experts opine that a safer alternative design for the Prolene mesh in TVT and TVT-O is to fashion Ultrapro mesh into a sling to treat SUI. To support this opinion, they are only able to point to a single study: Okulu 2014. In this study, an Ultrapro mesh fashioned into a sling was compared to similar slings made of Vypro and Prolene Soft mesh. None of these meshes were utilized with the TVT or TVT-O inserters and other tools. Significantly, in the Ultrapro, an erosion was noted after mesh implant, resulting in an erosion rate in this small patient population (n=48) of >2.0%. This does not demonstrate an increase in safety. Nor does relying on a single, small study to support their opinion equate to sound methodology when they disregard the consensus of thousands of polypropylene sling studies that conclude that those products are safe and efficacious. Moreover, plaintiffs’ experts’ opinion that a lightweight mesh is a safer alternative design for treating SUI ignores the fact that Ethicon attempted to manufacture a lightweight mesh (Project TOPA) but this effort resulted in six failed cadaver labs and the FDA’s rejection of its clearance application.

Degradation and Particle Loss

There is no clinical significance to claims of alleged particle loss and mesh degradation over time. AUGS and SUFU, which combined represent over 2,300 members, recently addressed the allegation that polypropylene mesh degrades. They concluded:

**MICHAEL KARRAM MD FACOG FPMRS
UROGYNECOLOGY AND GYNECOLOGIC SURGEON
SEVEN HILLS WOMENS HEALTH CENTERS
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Polypropylene is a stable and well-accepted biomaterial with a history of over five decades of use in mesh implants. In recent years, concerns regarding implanted polypropylene degradation have been raised as a result of very high magnification images that show portions of some explanted synthetic meshes with “cracked” surfaces. These surface changes were further hypothesized to lead to adverse clinical outcomes, though this is not supported by the extensive peer-reviewed literature related to polypropylene mesh repairs. Prospective studies have followed patients with implanted mid-urethral slings for 17 years and show excellent durability and safety of the procedure.

I agree with this conclusion. Claims that mesh degrades and that particle loss is a matter of clinical significance is not supported by any level 1 evidence, nor have I experienced any complications attributable to alleged particle loss or degradation in my 20 years of clinical practice.

Laser and Mechanically Cut Mesh

Likewise, there is not a clinically significant difference between mesh that is cut mechanically or by a laser. Ethicon still sells both mechanically cut and laser cut TVT products in order to satisfy surgeon preferences. I have used both. There has been rigorous clinical data from implants prepared using the two different techniques. There has been robust opportunity to assess for any difference in outcomes. None have been observed. Overall, this theoretical risk has led to no measurable clinical effect or risk. This conclusion is demonstrated by the fact that after 2007, which is when Ethicon first marketed TVT and TVT-O with a laser cut mesh, there is appreciable difference in complication or success rates in the body of medical literature between TVT/TVT-O studies before and after 2007. The uniformity of complication and success rates in the medical literature verifies that Ethicon’s conclusion that there is no clinically significant difference between laser and mechanically cut mesh was correct (ETH.MESH.01784823-28).

In summary, my opinion of the TVT procedure is very favorable. It is a simple, minimally invasive technique, excellent results, excellent patient satisfaction and outcomes. The

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UROGYNECOLOGY AND GYNECOLOGIC SURGEON
SEVEN HILLS WOMENS HEALTH CENTERS
CINCINNATI, OHIO**

risks are minimal compared to the more invasive surgeries we performed before the introduction of TVT. The complications are easy to manage and usually have good results as well. All patients are consented and understand the risks, benefits, options, complications, side effect, and results. In my opinion it is the first line surgical option for SUI. The large volume of data available support this idea and it continues to be the procedure of choice in the majority of surgeons that perform SUI surgeries.

I reserve the right to change my opinion if data contrary to the available data is presented.

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June 3, 2016